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Palladium N-heterocyclic carbene catalyzed regioselective C-H halogenation of 1-Aryl-3-methyl-1H-pyrazol-5(4H)-ones using N-halosuccinimides (NXS)

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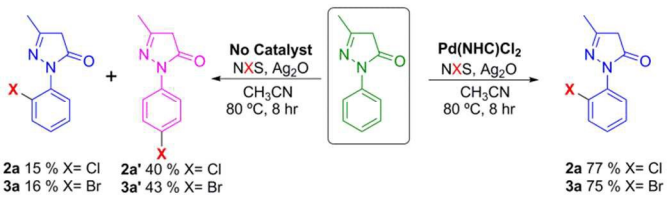
A novel palladium N-heterocyclic carbene [Pd(NHC)Cl_2] complex of Vitamin B_1 was synthesized and characterized by ^{1}H NMR, EDX, FT-IR and UV–visible spectroscopy. The complex was used as a catalyst for the regioselective *ortho*- C–H chlorination/bromination of 1-Aryl-3-methyl-1H-pyrazol-5(4H)-ones via C-H bond activation utilizing Ag_2O as the effective terminal additive. The catalyst was easy to prepare, efficient and was found to be highly regioselective to afford the target products in moderate to excellent yield.

1. Introduction

Recently, palladium-catalyzed functionalization of C−H bonds has emerged as a valuable, atom- and step-economical tool to construct C−C and C−heteroatom (O, N, Cl, Br, I) bonds proximal to the directing group with high regioselectivity.[1] Synthetic efforts have focused on several C-H activation reactions including arylation,[2] olefination,[3] oxygenation,[4] amination,[5] phosphonation,[6] sulfonylation[7] and halogenations[8] of both sp^2 and sp^3 C-H bonds. Amongst them, Pd-catalyzed selective *ortho*-sp^2 C-H halogenation reactions[8] have drawn much interest because aromatic halides are extremely valuable intermediates for synthetic elaboration.

Significant efforts have been made for selective *ortho*-halogenation of sp^2 C-H bonds by exploiting directing groups such as pyridines,[8a] cyano,[8d] aryl azo,[8e] acylaminos,[9] oxime ethers,[8c] carbamates[10] and various N-heterocycles. In some cases, the directing group needs to be pre-built-in and then removed afterwards.[8c] 3-Methyl-1-phenyl-1H-pyrazol-5(4H)-one **1a** itself is a neuroprotective drug known as Edaravone[11] which is used for the treatment of patients in acute stage of cerebral infarction brain ischemia. Therefore, our present study on C–H halogenations of compound **1a** will not only lead to a new regioselective protocol, but also provides new analogues of the existing drug **1a** for immediate drug screening. To the best of our knowledge, Pd-catalyzed C–H halogenation of **1a** has not been reported yet. The pyrazol-5(4H)-one fragment in **1a** acts as the intrinsic directing group.

Since the seminal discovery of first N-heterocyclic carbene (NHC) by Arduengo,[12] NHC-transition metal complexes have attracted considerable attention in the fields of organometallic chemistry and catalysis.[13] Due to strong σ-donating and little π-back bonding ability to stabilize the complexes, NHCs can generally be seen as alternatives to the widely used phosphine ligands.[14] Various complexes of palladium with NHC ligands have been prepared for coupling reactions.[15] Notably, all the pioneering work was limited to imidazolium based NHC ligands which were toxic, poorly biodegradable[16] and complicated to synthesize through multiple steps.[17] Various complexes of Pd(II) with NHC ligands have been prepared for



Scheme 1. Catalyst effect on ortho/para-halogenation selectivity

coupling reactions.[18] By taking the advantage of thiamine hydrochloride (VB_1) over imidazolium NHC ligands, recently we have synthesized a novel copper(N-heterocyclic

carbene)chloride [Cu(NHC)Cl] complex of Vitamin B_1 for three component click reaction.[19]

In continuation to our previous efforts,[19-20, 22] herein we report first ever synthesis and characterization of novel Pd(NHC)Cl_2 complex of Vitamin B_1 and its catalytic application for the regioselective C–H halogenations (Cl, Br) of 3-methyl-1-aryl-1H-pyrazol-5(4H)-ones using *N*-halosuccinimides (NXS). The protocol was found to be simple, efficient and highly regioselective to afford the target products in moderate to excellent yield.

2. Results and discussion

2.1 Characterization of catalyst.

The synthesized Pd(NHC)Cl_2 catalyst was thoroughly characterized by ^{1}H NMR, FT-IR, EDX and UV−visible spectroscopy. FT-IR spectrum of the catalyst exhibited absorption bands at 1620 (C=N stretch) and 3630 cm^{-1} (OH stretch). The characteristic amino stretching vibration bands were observed at 3340 and 3315 cm^{-1}. N-H bending absorption appeared at 1665 cm^{-1}. The EDX spectrum for the catalyst showed the existence of sulphur, chlorine and palladium elements (Figure 1) and confirmed the weight % of C, N, O, S, Pd and Cl respectively as 31.06, 13.06, 2.92, 8.31, 25.41 and 17.23 as expected with the calculated values of 32.56, 12.66, 3.61, 7.24, 24.04 and 16.02. The UV−visible spectra of free NHC ligand and the catalyst in distilled DMSO exhibited absorption bands at 268 and 275 nm respectively (Figure 2). The bathochromic shift in absorption spectrum may be assigned to complexation of NHC ligand with palladium.

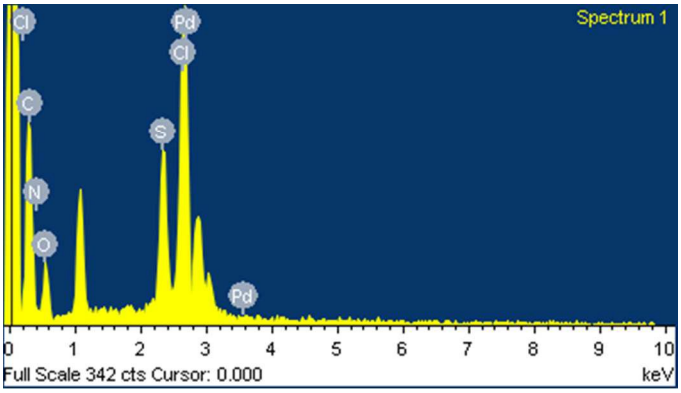


Figure 1. EDX analysis of Pd(NHC)Cl_2

Table 1. Catalyst screening for the synthesis[a] **2a**

Entry	Catalyst	mol %	Time[b] (h)	Yield[c] (%)
1	Nil	-	12	n.d.
2	Pd(NHC)Cl_2	10	8	77
3	Pd(NHC)Cl_2	5	8	77
4	$Pd(OAc)_2$	5	10	71
5	$PdCl_2$	5	9	69
6	$Pd(PPh_3)_4$	5	8	60

[a]Reaction conditions: 3-Methyl-1-phenyl-1H-pyrazol-5(4H)-one (1 mmol), NCS (1.1 mmol), Ag_2O (0.5 mmol) Pd- catalyst (5 mol %), acetonitrile (2 mL) and 80 ºC. [b]All the reactions were monitored by TLC using hexane : ethyl acetate (1:1). [c]Isolated yield, n.d., not detected.

2.2 Optimization of reaction conditions

Initially, the optimization of the reaction conditions for Pd(NHC)Cl_2 catalyzed halogenation was carried out using 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one **1a** as a model substrate with N-chlorosuccinimide (NCS) as a halogen source in presence of NHC, various additives and solvents. The reaction proceeded smoothly to give desired product **2a** in good to moderate yields with exclusive *ortho*-selectivity. It was surprisingly noted that in absence of the Pd catalyst, a mixture of *orhto*- (**2a**) and *para*-chloro (**2a'**) products were formed in very poor yields (Scheme 1). Two such bromo derivatives were obtained with NBS as the halogen source. The effectiveness of the model reaction was tested against various Pd-sources (Table 1). Among them, Pd(NHC)Cl_2 was found to be the most effective over other palladium species such as $Pd(OAc)_2$, $PdCl_2$ and $Pd(PPh_3)_4$. 5 mol % catalyst loading was observed to give the product **2a** in 77 % yield (Table 1, entry 3). To investigate the effects of solvent, the model reaction was performed in various solvents at 80 ºC using 5 mol % Pd(NHC)Cl_2 as the catalyst and 0.5 mmol of different additives (Table 2). It was observed that MeCN showed clearcut advantage over the other organic solvents having 77 % yields of **2a** (Table 2, entry 6) in 8 h. In order to improve the yield, effect of some additives such as Ag_2O, Ag_2SO_4, Ag_2CO_3, $K_2S_2O_8$ and oxone was checked (Table 2). In absence of any added additives only 36 % yield of **2a** was obtained (Table 2, entry 1) but the presence of 0.5 mmol Ag_2O improved the yield of **2a** up to 77 % (Table 2, entry 6). Thus, the optimized reaction condition was set as 5 mol % of Pd(NHC)Cl_2 as the catalyst with Ag_2O as an additive in MeCN at 80 ºC using 1 mmol of 1-arylpyrazolone and 1.1 mmol of NXS.

Table 2. Optimization of the reaction conditions for the synthesis[a] of **2a**

Entry	Additive	Solvent	Time[b] (h)	Yield[c] (%)
1	-	MeCN	12	36
2	Ag_2O	Toluene	8	40
3	Ag_2O	DMF	8	36
4	Ag_2O	Dioxane	8	25
5	Ag_2O	AcOH	8	70
6	Ag_2O	MeCN	8	77
7	Ag_2SO_4	MeCN	10	62
8	Ag_2CO_3	MeCN	10	60
9	$K_2S_2O_8$	MeCN	10	36
10	Oxone	MeCN	10	42

[a]Reaction conditions: 3-Methyl-1-phenyl-1H-pyrazol-5(4H)-one (1 mmol), NCS (1.1 mmol), Ag_2O (0.5 mmol) Pd(NHC)Cl_2 (5 mol %), solvent (2 mL) and 80 ºC. [b]All the reactions were monitored by TLC using hexane : ethyl acetate (1:1). [c]Isolated yield.

Based on previous studies, the mechanistic investigation of Pd(NHC)Cl_2 catalyzed regioselective C-H halogenation of **1a** has been assumed to involve a Pd(II) – Pd(IV) catalytic cycle.[8c, 21] Although, the role of Ag_2O was seemed to be very crucial. It might have acted as an oxidant or a co-catalyst. The plausible mechanism is suggested in Scheme 2. Ag_2O may oxidize the *ortho*- C-H bond of **1a** to form the intermediate **A**. **A** may then undergo transmetallation with Pd(NHC)Cl_2 to yield Pd(II) complex **B**, which after oxidative addition of NXS forms a

Pd(IV) intermediate **C**. Finally, halogenated product **2a** (or **3a**) is obtained via reductive elimination of **C**, followed by regeneration of the Pd(II) catalyst.

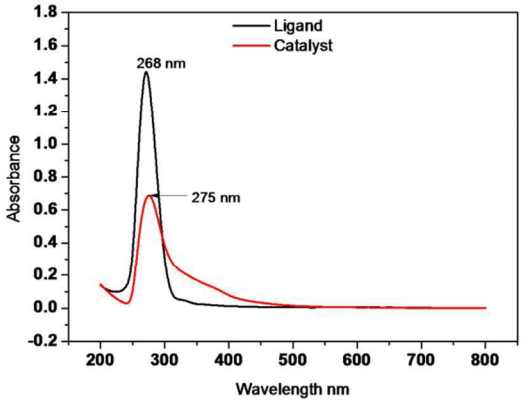
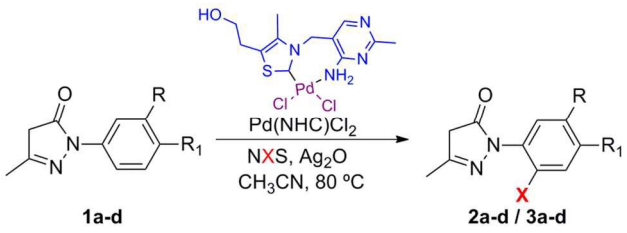


Figure 2. UV–visible spectra of free NHC ligand and catalyst.

Table 3. $Pd(NHC)Cl_2$ catalyzed regioselective C-H halogenation of 1-Aryl-3-methyl-1H-pyrazol-5(4H)-ones[a] **1a-d.**



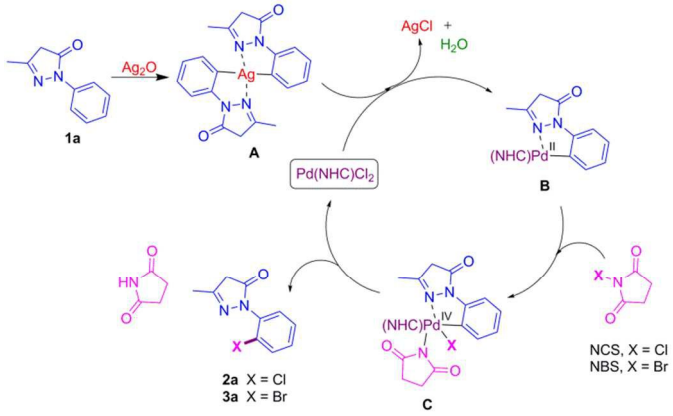
Entry	Compounds	R	R_1	X	Time[b] (h)	Yield[c] (%)
1	2a	-H	-H	-Cl	8	77
2	2b	-Cl	-H	-Cl	8.5	75
4	2c	-H	$-CH_3$	-Cl	8.5	70
3	2d	-H	-Cl	-Cl	9	73
5	3a	-H	-H	-Br	8	76
6	3b	-Cl	-H	-Br	8.5	72
8	3c	-H	$-CH_3$	-Br	9	72
7	3d	-H	-Cl	-Br	9	74

[a]Reaction conditions: 1-arylpyrazolones (1 mmol), NXS (X = Cl or Br, 1.1 mmol), Ag_2O (0.5 mmol) $Pd(NHC)Cl_2$ (5 mol %), acetonitrile (2 mL) and 80 °C. [b]All the reactions were monitored by TLC using hexane : ethyl acetate (1:1). [c]Isolated yield.

With the optimized reaction conditions in hand, a scope of the $Pd(NHC)Cl_2$ catalyzed regioselective C-H halogenation reaction was investigated with a diverse array of substituted 1-Aryl-3-methyl-1H-pyrazol-5(4H)-ones **1a-d** (Table 3). The substrates bearing electron-donating or –withdrawing substituents on the aryl ring reacted smoothly to afford the desired products in good to moderate yields. All the results are summarized in Table 3. The structures of all the synthesized compounds were well characterized by NMR spectroscopy.

3. Conclusion

A novel $Pd(NHC)Cl_2$ catalyst has been developed for the regioselective *ortho*- C–H chlorination/ bromination of 1-Aryl-3-methyl-1H-pyrazol-5(4H)-ones utilizing N-halosuccinimide as the halogenating reagent and Ag_2O as the effective additive via C–H bond activation. The protocol was found to be simple, efficient and highly regioselective to afford the target products in moderate to excellent yield. Moreover, the present study had not only led to the regioselectivity, but also provided valuable synthetic building blocks in organic synthesis.



Scheme 2. Plausible catalytic cycle for the regioselective C-H halogenation of 3-Methyl-1-phenyl-1H-pyrazol-5(4H)-one.

4. Experimental section

All the chemicals were purchased from Sigma Aldrich and used as received. All organic solvents used were of analytical grade and used without further purification. All the reactions were monitored by thin-layer chromatography carried out on fluorescent coated plates (aluminium plates coated with silica gel 60 F254, 0.25 mm thickness, Merck) and detection of the components was made by exposure to UV light. NMR spectra were recorded in $CDCl_3$ on Bruker Avance 400 MHz spectrometer. The chemical shifts are reported in δ parts per million. IR spectra were recorded on a FTIR PerkinElmer Spectrum 100 spectrometer in KBr pellets with absorption in cm^{-1} at Sophisticated Instrumentation Centre for Applied Research & Training (SICART), Vallabh Vidyanagar. Elemental analysis was performed on PerkinElmer 2400 series-II elemental analyzer (PerkinElmer, USA) and all results are found within $\pm$0.4% of the theoretical compositions. IKA RV 10 control rotary evaporator was used to distill the solvents under vacuum. The EDX was performed using JOEL JSM-5610 scanning electron microscope (SEM).

4.1 Synthesis of palladium N-heterocyclic carbene complex

A 50 mL round bottom flask was charged with $Pd(OAc)_2$ (0.5 mmol), thiamine hydrochloride (vitamin B_1) (1 mmol), NaOt-Bu (1 mmol) and THF (5 mL). The mixture was stirred at room temperature for 3 h and then refluxed for additional 2 h. After cooling to room temperature, the resulting orange residue was filtered, washed with acetonitrile (2 × 5 mL) and dried under vacuum to afford the title compound with 80% yield.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.39 (s, 3H), 2.51(s, 3H), 3.05 (t, 2H), 3.65 (t, 2H), 5.47 (s, 2H), 7.40 (s, 2H), 8.11

(s, 1H), 9.60 (s, 1H). FT-IR (KBr): 3630, 3410, 3340, 3315, 3100, 1620, 1430, 1527, 1060, 780, 610 cm^{-1}

4.2 General procedure for the regioselective halogenation of 1-Aryl-3-methyl-1H-pyrazol-5(4H)-ones catalyzed by $Pd(NHC)Cl_2$

A mixture of 1-Aryl-3-methyl-1H-pyrazol-5(4H)-ones (1 mmol), NXS (X = Cl or Br, 1.1 mmol), Ag2O (0.5 mmol) and $Pd(NHC)Cl_2$ complex (5 mol %) in 2 mL acetonitrile was magnetically stirred at 80 ºC for the required time. The solvent was removed under vacuum and the resulting residues were purified by chromatography on silica gel column by using hexane : ethyl acetate (20 : 1, v/v) as eluent to afford the desired products.

4.3 Spectral data

4.3.1 1-(2-chlorophenyl)-3-methyl-1H-pyrazol-5(4H)-one (2a)

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.21 (s, 3H), 3.44 (s, 2H), 7.33-7.38 (m, 2H), 7.42-7.45 (m, 1H), 7.51-7.53 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.15 (CH_3), 41.47 (CH_2), 127.56, 128.85, 129.85, 130.56, 131.82, 134.44, 156.60 (C=N), 171.26 (C=O), FT-IR (KBr): 3104, 2810, 1623 (C=O str.), 1585 (C=N str.), 1494, 1311, 1218, 1035, 964 cm^{-1}, Anal. Calcd. for $C_{10}H_9ClN_2O$: C, 57.57; H, 4.35; N, 13.43. Found: C, 57.49; H, 4.26; N, 13.40.

4.3.2 1-(2,5-dichlorophenyl)-3-methyl-1H-pyrazol-5(4H)-one (2b)

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.21 (s, 3H), 3.43 (s, 2H), 7.31 (dd, J = 2.8 Hz, J = 8.4 Hz, 1H), 7.45 (t, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.15 (CH_3), 41.42 (CH_2), 128.67, 129.74, 129.98, 131.35, 132.95, 135.36, 157.04 (C=N), 170.95 (C=O), FT-IR (KBr): 3101, 2810, 1629 (C=O str.), 1582 (C=N str.), 1489, 1308, 1210, 1032, 967 cm^{-1}, Anal. Calcd. for $C_{10}H_8Cl_2N_2O$: C, 49.41; H, 3.32; N, 11.52. Found: C, 49.39; H, 3.18; N, 11.36.

4.3.3 1-(2-chloro-4-methylphenyl)-3-methyl-1H-pyrazol-5(4H)-one (2c)

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.21 (s, 3H), 2.36 (s, 3H), 3.44 (s, 2H), 7.28-7.35 (m, 2H), 7.73 (d, J = 3.6 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.05 (CH_3), 20.97(Ar-CH_3), 43.08 (CH_2), 128.67, 119.00, 126.06, 129.36, 134.78, 135.59, 145.10, 156.17 (C=N), 170.45 (C=O), FT-IR (KBr): 3107, 2810, 1625 (C=O str.), 1580 (C=N str.), 1484, 1315, 1214, 1032, 969 cm^{-1}, Anal. Calcd. for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; N, 12.58. Found: C, 59.22; H, 4.72; N, 12.35

4.3.4 1-(2,4-dichlorophenyl)-3-methyl-1H-pyrazol-5(4H)-one (2d)

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.19 (s, 3H), 3.50 (s, 2H), 7.98 (t, 1H), 8.33 (m, 1H), 9.15 (d, J = 2.4 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.15 (CH_3), 41.42 (CH_2), 128.68, 129.76, 129.98, 131.35, 132.95, 135.36, 157.04 (C=N), 170.95 (C=O), FT-IR (KBr): 3109, 2811, 1629 (C=O str.), 1583 (C=N str.), 1485, 1320, 1213, 1035, 967 cm^{-1}, Anal. Calcd. for $C_{10}H_8Cl_2N_2O$: C, 49.41; H, 3.32; N, 11.52. Found: C, 49.31; H, 3.17; N, 11.30.

4.3.5 1-(2-bromophenyl)-3-methyl-1H-pyrazol-5(4H)-one (3a)

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.22 (s, 3H), 3.46 (s, 2H), 7.15-7.18 (m, 1H), 7.32 (t, 1H), 7.83-7.86 (m, 1H), 7.95 (t, 1H), ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.02 (CH_3), 43.12 (CH_2), 116.47, 118.62, 124.87, 129.88, 134.57, 139.09, 156.63 (C=N), 170.53 (C=O), FT-IR (KBr): 3110, 2813, 1625 (C=O str.), 1580 (C=N str.), 1480, 1318, 1215, 1031, 969 cm^{-1}, Anal. Calcd. for $C_{10}H_9BrN_2O$: C, 47.46; H, 3.58; N, 11.07. Found: C, 47.40; H, 3.42; N, 10.98.

4.3.6 1-(2-bromo-5-chlorophenyl)-3-methyl-1H-pyrazol-5(4H)-one (3b)

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.20 (s, 3H), 3.43 (s, 2H), 7.31 (dd, J = 2.4, Hz, J = 8.8 Hz, 1H), 7.44 (t, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.15 (CH_3), 41.42 (CH_2), 120.00, 128.67, 129.74, 129.98, 131.35, 135.35, 157.06 (C=N), 170.96 (C=O), FT-IR (KBr): 3107, 2811, 1625 (C=O str.), 1582 (C=N str.), 1481, 1315, 1214, 1030, 969 cm^{-1}, Anal. Calcd. for $C_{10}H_8BrClN_2O$: C, 41.77; H, 2.80; N, 9.74. Found: C, 41.57; H, 2.71; N, 9.55.

4.3.7 1-(2-bromo-4-methylphenyl)-3-methyl-1H-pyrazol-5(4H)-one (3c)

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.21 (s, 3H), 2.36 (s, 3H), 3.44 (s, 2H), 7.18-7.27 (m, 2H), 7.74 (d, J = 4.4 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.04 (CH_3), 20.96(Ar-CH_3), 43.07 (CH_2), 128.67, 119.00, 120.90, 129.35, 134.77, 134.78, 135.60, 156.15 (C=N), 170.44 (C=O), FT-IR (KBr): 3108, 2810, 1622 (C=O str.), 1585 (C=N str.), 1480, 1315, 1212, 1030, 967 cm^{-1}, Anal. Calcd. for $C_{11}H_{11}BrN_2O$: C, 49.46; H, 4.15; N, 10.49. Found: C, 49.41; H, 3.97; N, 10.34.

4.3.8 1-(2-bromo-4-chlorophenyl)-3-methyl-1H-pyrazol-5(4H)-one (3d)

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.21 (s, 3H), 3.43 (s, 2H), 7.33 (dd, J = 2.4, Hz, J = 8.8 Hz, 1H), 7.44 (t, 2H), ^{13}C NMR (100 MHz, CDCl3): δ (ppm) 16.22 (CH_3), 44.51 (CH_2), 116.57, 123.42, 130.06, 134.46, 145.01, 157.04 (C=N), 169.26 (C=O), FT-IR (KBr): 3102, 2810, 1625 (C=O str.), 1585 (C=N str.), 14804, 1314, 1210, 1032, 968 cm^{-1}, Anal. Calcd. for $C_{10}H_8BrClN_2O$: C, 41.77; H, 2.80; N, 9.74. Found: C, 41.67; H, 2.69; N, 9.65.

4.3.9 1-(4-chlorophenyl)-3-methyl-1H-pyrazol-5(4H)-one (2a')

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.22 (s, 3H), 3.46 (s, 2H), 7.36 (dd, J = 2.4, Hz, J = 7.2 Hz, 2H), 7.86 (dd, J = 2.0, Hz, J = 6.8 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.06 (CH_3), 43.10 (CH_2), 119.87, 128.87, 131.59, 135.99, 156.19 (C=N), 170.45 (C=O), FT-IR (KBr): FT-IR (KBr): 3110, 2815, 1620 (C=O str.), 1582 (C=N str.), 1486, 1315, 1210, 1032, 966 cm^{-1}, Anal. Calcd. for $C_{10}H_9ClN_2O$: C, 57.57; H, 4.35; N, 13.43. Found: C, 57.51; H, 4.22; N, 13.13.

4.3.10 1-(4-bromophenyl)-3-methyl-1H-pyrazol-5(4H)-one (3a')

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.22 (s, 3H), 3.45 (s, 2H), 7.49-7.53 (m, 2H), 7.79-7.83 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.07 (CH_3), 43.12 (CH_2), 119.00, 120.16, 131.82, 138.22, 156.04 (C=N), 170.94 (C=O), FT-IR (KBr): 3105, 2811, 1625 (C=O str.), 1583 (C=N str.), 1490, 1310, 1218, 1035, 967 cm^{-1}, Anal. Calcd. for $C_{10}H_9BrN_2O$: C, 47.46; H, 3.58; N, 11.07. Found: C, 47.33; H, 3.41; N, 10.91.

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Notes

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The spectral data of synthesized compound are shown in supplementary data.

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